NDA 22-081 Letairis® (ambrisentan)

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404

I. GOAL(S):

The goals of the Letairis Risk Evaluation and Mitigation Strategy (REMS) Program are:

1. To inform prescribers, patients, and pharmacists about the serious risk of teratogenicity and safe-use conditions for Letairis

2. To minimize the risk of fetal exposure and adverse fetal outcomes in Females of Reproductive Potential (FRP) prescribed Letairis

    a. Females who are pregnant must not be prescribed Letairis

    b. Females taking Letairis must not become pregnant

II. REMS ELEMENTS

A. Medication Guide

A Medication Guide will be dispensed with each Letairis prescription in accordance with 21CFR 208.24.

The Medication Guide is part of the REMS and is appended.

B. Elements To Assure Safe Use

1. Healthcare providers who prescribe Letairis will be specially certified.

    a. Gilead will ensure that physicians and other appropriately licensed healthcare professionals who prescribe Letairis are specially certified. Gilead will ensure that, to become certified, each prescriber agrees, on the *Prescriber Enrollment and Agreement Form*, that he or she has read the full prescribing information (PI), the *Letairis Medication Guide*, and the *Prescriber Guide to the Letairis REMS Program*. The physician further agrees that he or she will:

        i) Enroll all females in the Letairis REMS program

        ii) Determine whether each female is of reproductive potential as defined in the *Prescriber Guide to the Letairis REMS Program*

iii) Advise all females that Letairis is only available through a restricted distribution program called the Letairis REMS program

iv) For FRP:

(1) Educate FRPs about the risk of teratogenicity, the need to use highly reliable contraception as defined in the *Prescriber Guide to the Letairis REMS Program* during Letairis treatment and for one month following treatment discontinuation, and the need to use emergency contraception if required

(2) Order and review pregnancy tests prior to initiation of Letairis treatment, monthly during treatment, and for one month after stopping Letairis treatment

(3) Counsel a female patient if she is not complying with the required testing or if she is not using appropriate contraception as specified for FRP

(4) Review with FRP, the *Letairis Medication Guide* and the *Letairis REMS Program Guide for Females Who Can Get Pregnant* prior to initiating treatment

(5) Report any changes in reproductive status by completing the *Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form* within 10 business days of becoming aware of the change

v) For Pre-Pubertal Females:

(1) Educate Pre-Pubertal Female patient and parent/guardian about the risk of teratogenicity

(2) Review the *Letairis Medication Guide* with the patient and parent/guardian

(3) Regularly evaluate Pre-Pubertal Females for any change in reproductive status while receiving Letairis

(4) Verify and document status as Pre-Pubertal Female at least annually for Pre-Pubertal Females who are at least 8 years of age and older by completing the *Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form*

(5) Report any change in reproductive status by completing the *Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form* within 10 business days of becoming aware of the change

vi) For Post-Menopausal Females:

(1) Report any misclassification in reproductive potential status by completing the *Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form* within 10 business days of becoming aware.

vii) Report adverse events and any pregnancies during Letairis treatment to Gilead with all available information required for the Form FDA 3500A

viii) For Females with Other Medical Reasons for Permanent, Irreversible Infertility:

(1) Report any misclassification in reproductive potential status by completing the *Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form* within 10 business days of becoming aware.

(2) Report adverse events and any pregnancies during Letairis treatment to Gilead with all available information required for the Form FDA 3500A.

b. Gilead will:

i) Ensure that prescribers' enrollment information and date of agreement are linked to their enrolled female patients' information in a validated database

ii) For all females, ensure that the patient information from a new prescriber is linked in the Letairis REMS program database with information from the prior prescriber

iii) Ensure that the Letairis REMS Coordinating Center annually contacts the prescriber of a Pre-Pubertal Female to ensure that the prescriber verifies the Pre-Pubertal Female's reproductive status by completing the *Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form*

iv) Maintain a validated database of certified prescribers in the Letairis REMS program. Gilead will ensure that prescribers' certification requirements are met and may de-enroll noncompliant prescribers until the requirements are met

v) Ensure that within 60 days of REMS modification approval, all materials listed in or appended to the Letairis REMS will be available through the Letairis REMS program website (www.letairisrems.com) or by calling the Letairis REMS Coordinating Center at 1-866-664-5327

c. The following materials are part of the Letairis REMS program and are appended:

i) *Prescriber Enrollment and Agreement Form*

ii) *Prescriber Guide to the Letairis REMS Program*

iii) *Letairis REMS Program Guide for Females Who Can Get Pregnant*

iv) *Patient Enrollment and Consent Form*

v) *Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form*

vi) *Letairis REMS website (www.letairisrems.com)*

2. Pharmacies, practitioners, and health care settings that dispense Letairis (dispensers) will be specially certified.

    a. Gilead will ensure that pharmacies, practitioners, and health care settings that dispense Letairis are specially certified. Gilead will ensure that, to be certified, pharmacies, practitioners, and health care settings that dispense Letairis attest that:

        i) For all female patients, they will dispense Letairis only to patients enrolled in the Letairis REMS program

        ii) Certified pharmacies will dispense Letairis to female patients only after receipt of patient enrollment form from the Letairis REMS Coordinating Center

        iii) Certified pharmacies will confirm any change in a female patient's reproductive potential status through the Letairis REMS Coordinating Center

        iv) Provide a *Letairis Medication Guide* to patients each time Letairis is dispensed

        v) For FRP (as defined in the *Prescriber Guide to the Letairis REMS Program*):

            (1) Counsel FRP on the risk of serious birth defects and the need to use highly reliable contraception (as defined in the *Prescriber Guide to the Letairis REMS Program*) during Letairis treatment and for one month after stopping Letairis treatment

            (2) Inform FRP of the need to complete a monthly pregnancy test and to inform their prescriber immediately if they suspect they may be pregnant

            (3) Speak with each FRP, or their prescriber, every month before dispensing Letairis to obtain confirmation that pregnancy testing was completed

            (4) Dispense Letairis to FRP no more than a 30-day supply and only upon completing the following process:

                (a.) Obtain confirmation from FRP that the pregnancy testing was completed

                (b.) If unable to obtain confirmation from FRP that the pregnancy testing was completed, or if the FRP cannot be reached, the certified pharmacy will obtain confirmation from the patient's prescriber

                (c.) If the prescriber for the FRP cannot confirm that the pregnancy testing was completed, the certified pharmacy will:

                    i. Remind the prescriber of his/her obligation to order and review monthly pregnancy tests

ii. Ask the prescriber whether or not he/she authorizes the refill of Letairis. The FRP is eligible to receive a 30-day supply of Letairis only if the prescriber authorizes the refill of Letairis

vi) Notify Gilead of reports of adverse events and any reports of pregnancy and provide all available information needed for FDA Form 3500A

vii) Certified pharmacies will provide daily product dispensing data for FRP to the Letairis REMS Coordinating Center

b. Gilead will ensure the Letairis REMS Coordinating Center notifies certified pharmacies of patients' change in reproductive status within one business day of receipt of completed *Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form*

c. Gilead will ensure that a designated representative of each certified pharmacy:

i) Is trained on the requirements of the Letairis REMS program

ii) Trains dispensing staff on the Letairis REMS program procedures and Letairis REMS materials as described above prior to dispensing Letairis to FRP

iii) Agrees that the certified pharmacy may be audited by the FDA, Gilead, or a third party designated by Gilead

3. Letairis will be dispensed to FRP with evidence or other documentation of safe-use conditions:

a. Gilead will ensure that FRP treated with Letairis are enrolled in the Letairis REMS program and assigned a unique patient identification number, before Letairis is dispensed by a certified pharmacy. Gilead will ensure that, to become enrolled, or when changing prescribers, each FRP must sign a *Patient Enrollment and Consent Form* acknowledging that she has read the *Letairis Medication Guide* and the *Letairis REMS Program Guide for Females Who Can Get Pregnant*. By enrolling, the FRP agrees:

i) To be contacted, prior to each shipment of Letairis, to obtain confirmation that pregnancy testing was completed

ii) To be counseled on the requirements of the Letairis REMS program and the risks of Letairis

iii) To be contacted by Gilead or the Letairis REMS Coordinating Center if she becomes pregnant while on Letairis or within 30 days after treatment discontinuation

C. Implementation System

The Implementation System will include the following:

1. Gilead will maintain a validated database of certified dispensers and females enrolled in the Letairis REMS program to monitor and evaluate implementation of the elements provided for under Sections B.2 and B.3 above

2. Gilead will monitor the distribution of Letairis to ensure that the drug is only shipped to certified dispensers.

3. Gilead will track Letairis dispensing and review the location and amount of medication dispensed by certified pharmacies to FRPs.

4. Gilead will audit all certified pharmacies and the Letairis REMS Coordinating Center at the initiation of the Letairis REMS program to ensure they implement the program as directed. Thereafter, Gilead will include the certified pharmacies and the Letairis REMS Coordinating Center in the company's annual audit plan

5. Gilead will monitor and evaluate the implementation of the elements provided for under Sections B.1, B.2, and B.3, above, in the manner described in the Letairis REMS Supporting Document, and take reasonable steps to work to improve implementation of these elements

6. Gilead will monitor the certified pharmacies to ensure their compliance with the Letairis REMS program and will institute corrective actions if they are found non-compliant

D. Timetable for Submission of Assessments

Gilead will submit Letairis REMS assessments to the FDA annually no later than August 13th. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that REMS assessment. Gilead will submit each REMS assessment so that it will be received by the FDA on or before the due date.

Letairis Risk Evaluation and Mitigation Strategy (REMS) Program

Prescriber Enrollment and Agreement Form

To be enrolled into the Letairis REMS Program, complete and fax this form.
FAX THIS FORM TO: 1-888-882-4035

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1 Prescriber Information

First Name: _____ Middle Initial: _____ Last Name: _____
Suffix: _____

Specialty: _____ Name of Facility: _____

Office Contact (First and Last Name): _____

Address: _____ City: _____ State: _____ ZIP: ___

E-mail: _____ Phone: (____)_____ Fax: (____)_____

State License #: _____ NPI #: _____

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2 Prescriber Agreement

By signing below, you signify your understanding of the risks of Letairis® (ambrisentan) treatment and your obligation as a Letairis prescriber to educate your female patients about these risks, counsel them on risk reduction, monitor them appropriately, and report adverse events to the Letairis REMS Coordinating Center. Specifically, you attest to the following:

- I have read the full Prescribing Information, the *Letairis Medication Guide*, and the *Prescriber Guide for the Letairis REMS Program* and agree to comply with the Letairis REMS Program requirements
- I agree to enroll all female patients into the Letairis REMS Program
- I will determine the reproductive potential status of all female patients using the definitions provided in the *Prescriber Guide for the Letairis REMS Program*
- I will advise all female patients that Letairis is only available through a restricted distribution program called the Letairis REMS Program
- I will counsel Females of Reproductive Potential on the risks of Letairis, including the risk of serious birth defects, and review the *Letairis Medication Guide* and the *Letairis REMS Program Guide for Females Who Can Get Pregnant* with the patient
- I will counsel the Pre-Pubertal Female patient and parent/guardian on the risks of Letairis, including the risk of serious birth defects, and review the *Letairis Medication Guide* with the patient and parent/guardian
- I will verify the reproductive potential status annually for Pre-Pubertal Females who are 8 years of age and older
- I will order and review pregnancy tests for Females of Reproductive Potential prior to initiating treatment with Letairis, monthly during treatment, and for 1 month after stopping treatment
- I agree to report any change in reproductive potential status by submitting a *Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form* within 10 business days of becoming aware of the change
- I will counsel Females of Reproductive Potential to use highly reliable contraception during Letairis treatment, and for 1 month after stopping treatment, and the need to use emergency contraception if required
- I will counsel female patients who fail to comply with the Letairis REMS Program requirements
- I will notify the Letairis REMS Coordinating Center of any adverse events, or if any patient becomes pregnant during Letairis treatment or within 1 month after stopping treatment

REQUIRED	Prescriber Signature: X	Date:

Please visit **www.letairisrems.com** or call **1-866-664-5327** for more information about the Letairis REMS Program.

Letairis
ambrisentan
5 mg and 10 mg Tablets

LETAIRIS RISK EVALUATION AND MITIGATION STRATEGY (REMS)

Prescriber Guide for the Letairis REMS Program

Changes to the Letairis Risk Evaluation and Mitigation Strategy (REMS) Program (October 2014)

- New definition of Female of Non-Reproductive Potential (page 4)
- Revised form: *Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form* (page 6)

This guide is part of an FDA-approved REMS.

Letairis® ambrisentan
5 mg and 10 mg Tablets

Reference ID: 3650027

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Letairis REMS Program

Indication

Letairis is an endothelin receptor antagonist (ERA) indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability and delay clinical worsening. Studies establishing effectiveness included predominantly patients with WHO Functional Class II-III symptoms and etiologies of idiopathic or heritable PAH (64%) or PAH associated with connective tissue diseases (32%).

Risk of teratogenicity

Letairis is contraindicated in females who are pregnant, as Letairis may cause fetal harm when administered to a pregnant female. There are no data regarding the use of Letairis in pregnant females; the possibility of serious birth defects in humans cannot be excluded.

Pregnancy must be excluded prior to the initiation of Letairis treatment, monthly thereafter, and for 1 month after stopping treatment.

Letairis REMS Program

Because of the risk of serious birth defects, Letairis is only available to females through a restricted distribution program under an FDA-required REMS. The Letairis REMS Program helps ensure the benefits of Letairis outweigh the risk of teratogenicity. The purposes of the Letairis REMS Program are to:

- Inform and educate healthcare providers and female patients about the risk of teratogenicity associated with the use of Letairis
- Minimize the risk of fetal exposure and adverse fetal outcomes in Females of Reproductive Potential
  - Females who are pregnant must not be prescribed Letairis
  - Females taking Letairis must not become pregnant

Changes to the Letairis REMS Program

- New definition of Females of Non-Reproductive Potential
- Revised form: *Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form*

Overview of the Letairis REMS Program

- Letairis is only available to females through a restricted distribution program
- Prescribers must enroll in the Letairis REMS Program and comply with the Letairis REMS Program requirements to prescribe Letairis
- All female patients must enroll in the Letairis REMS Program to receive Letairis
- Prescribers must educate and counsel Females of Reproductive Potential and Pre-Pubertal Females on the risks of Letairis, including the risk of serious birth defects. The parent/guardian of the Pre-Pubertal Female must also be educated and counseled on the risks of Letairis.
- Prescribers must order and review pregnancy tests for Females of Reproductive Potential prior to initiation of treatment, monthly during treatment, and for 1 month after stopping treatment

Summary of the Letairis REMS Program Requirements by Patient Category

Requirement	Female of Reproductive Potential	Female of Non-Reproductive Potential		
		Pre-Pubertal	Post-Menopausal	Other medical reasons for permanent, irreversible infertility
Prescriber enrolls female patients into Letairis REMS Program	X	X	X	X
Counseling with *Letairis REMS Program Guide for Females Who Can Get Pregnant*	X			
Counseling with *Letairis Medication Guide*, including the risk of teratogenicity	X	X*		
Prescriber must order and review pregnancy tests prior to initiation of treatment, monthly during treatment, and for 1 month after stopping treatment	X			
Prescriber must verify reproductive status annually by completing the *Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form* for females who are at least 8 years of age and older		X		

Prescriber must complete the *Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form* upon becoming aware of any change in reproductive potential status within 10 business days of awareness	X	X	X	X

*** Counsel Pre-Pubertal Female patient and parent/guardian**

Your Role in the Letairis REMS Program

Prescribers must complete the following steps in the Letairis REMS Program:

1. **Read the Letairis Prescribing Information and this guide to understand the Letairis REMS Program and the risks of Letairis**
2. **Complete the *Prescriber Enrollment and Agreement Form***
   - You will attest to understanding the risks of Letairis and agree to comply with the requirements of the Letairis REMS Program
3. **Determine the reproductive potential status of female patients**

Females of Reproductive Potential:

- Females of Reproductive Potential include girls who have entered puberty and all women who have a uterus and have not passed through Menopause (as defined in the following column)
- For the purposes of this REMS, puberty includes those girls who are at least Tanner Stage 3 and have not yet had a menses (premenarchal)

Females of Non-Reproductive Potential:

- **Pre-Pubertal Females:** Females who are at Tanner Stages 1 and 2 are not considered to be of reproductive potential
- **Post-Menopausal Females:** Females who have passed through Menopause (as defined below)
- **Females with other medical reasons for permanent, irreversible infertility**

Definition of Menopause:

- Menopause is defined as 12 months of spontaneous amenorrhea (not amenorrhea induced by a medical condition or medical therapy) or post-surgical from bilateral oophorectomy

4. **Educate/counsel all female patients about risks of Letairis and about the Letairis REMS Program**
   - Advise all females that Letairis is only available through a restricted distribution program called the Letairis REMS Program

For Females of Reproductive Potential:

- Review with the Female of Reproductive Potential the *Letairis Medication Guide* and the *Letairis REMS Program Guide for Females Who Can Get Pregnant* prior to initiating treatment
- Educate Females of Reproductive Potential about the risk of teratogenicity, the need to use highly reliable contraception (see page 7) during Letairis treatment and for 1 month following treatment discontinuation, and the need to use emergency contraception, if required
- Order and review pregnancy tests prior to initiation of Letairis treatment, monthly during treatment, and for 1 month after stopping Letairis treatment
- Advise the patient of the requirement for monthly pregnancy tests to confirm they are not pregnant so they can receive Letairis
- Counsel the Female of Reproductive Potential if she is not complying with the Letairis REMS Program requirements
- Submit a *Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form* within 10 business days of becoming aware of any change in reproductive potential status

For Females of Non-Reproductive Potential:

For Pre-Pubertal Females:

- Educate the Pre-Pubertal Female patient and parent/guardian about the risk of teratogenicity and review the *Letairis Medication Guide* with the patient and parent/guardian
- Evaluate regularly Pre-Pubertal Females for any changes in reproductive status while receiving Letairis
- Verify the reproductive potential status annually for Pre-Pubertal Females who are at least 8 years of age and older by completing the *Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form*
- Report any misclassification or change in reproductive potential status by completing the *Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form* within 10 business days of becoming aware of the change

For Post-Menopausal Females:

- Report any misclassification in reproductive potential status by completing the *Change in Reproductive Potential Status and Pre-pubertal Annual*

Verification Form within 10 business days of becoming aware

For females with other medical reasons for permanent, irreversible infertility:

- Report any misclassification in reproductive potential status by completing the *Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form* within 10 business days of becoming aware

5. Check pregnancy status (in Female of Reproductive Potential)

- Order and review pregnancy tests for the patient:
  - Prior to initiating treatment
  - Monthly during treatment
  - 1 month after stopping treatment

The patient must agree to be contacted by the Certified Pharmacy prior to each shipment to confirm that a pregnancy test was completed, and she must also agree to be contacted by the Letairis REMS Coordinating Center if she becomes pregnant while on Letairis or within 1 month of stopping treatment.

6. Enroll all female patients into the Letairis REMS Program

- Complete a *Letairis Patient Enrollment and Consent Form*
- Confirm the female patient has agreed to comply with program requirements and has signed the form where indicated. Fax the completed form, along with all patient insurance information, including prescription drug benefits and medical benefits, to the Letairis REMS Coordinating Center at **1-888-882-4035**
- Keep the original form with the patient's records

7. Evaluate reproductive potential status of female patients throughout treatment

- Report any change in patient's reproductive potential status within 10 business days of becoming aware of the change to the Letairis REMS Coordinating Center by faxing the completed *Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form* to **1-888-882-4035**
- Verify the reproductive potential status of Pre-Pubertal Females who are 8 years of age or older annually by completing the *Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form*
- Counsel females who fail to comply with the Letairis REMS Program requirements
- Notify the Letairis REMS Coordinating Center of any adverse events, or if any patient becomes pregnant during Letairis treatment or within 1 month of stopping treatment

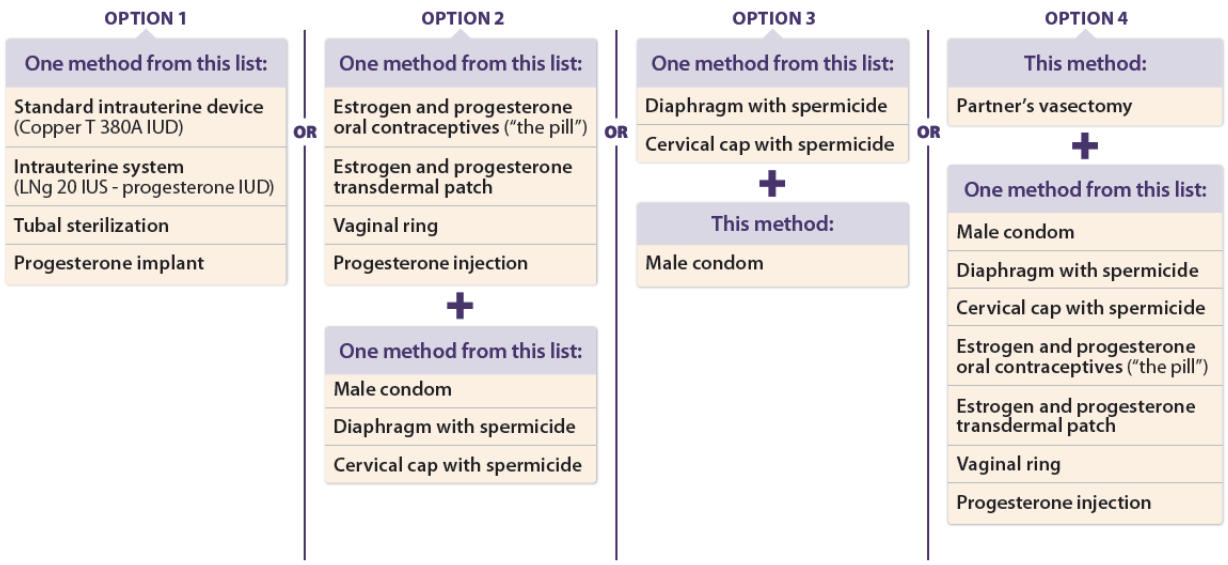
Contraceptive Options for Females of Reproductive Potential

- All Females of Reproductive Potential should undergo contraceptive counseling with either the prescriber or another designated healthcare practitioner trained in contraceptive counseling

Please refer to the diagram on the next page for a complete list of the acceptable contraceptive options. The same diagram also appears in the *Letairis REMS Program Guide for Females Who Can Get Pregnant* and should be used to discuss acceptable birth control options with patients.

- Educate and counsel Females of Reproductive Potential on the use of emergency contraception in the event of unprotected sex or known or suspected contraceptive failure
- Remind patients to report to you immediately any delay in having a period or any other reason of suspected pregnancy during treatment
- If pregnancy is suspected for any reason, a pregnancy test must be performed
- **The prescriber must notify the Letairis REMS Coordinating Center (by phone at 1-866-664-5327) of any pregnancies that occur during treatment or within 1 month of discontinuation**

Contraceptive Options for Females of Reproductive Potential



Role of Certified Pharmacies

- Contact all Females of Reproductive Potential receiving Letairis each month to confirm completion of pregnancy testing, and counsel them on the risk of teratogenicity
- Provide a copy of the *Medication Guide* to patients/caregivers each time Letairis is dispensed
- Ship Letairis to the patient/caregiver

For a list of Certified Pharmacies, visit **www.letairisrems.com** or call the Letairis REMS Coordinating Center at **1-866-664-5327**

The Letairis REMS Coordinating Center

- Enters every Letairis prescriber and female patient into the Letairis REMS Program database
- Collects all *Patient Enrollment and Consent Forms* and *Prescriber Enrollment and Agreement Forms*
- Sends patient information to the chosen Certified Pharmacy
- Collects information about adverse events, changes in reproductive status, annual verification of reproductive potential status for Pre-Pubertal Females, and any occurrences of pregnancies during Letairis treatment or within 1 month of treatment discontinuation

Notes

Additional questions

Please visit www.letairisrems.com or call the Letairis REMS Coordinating Center at 1-866-664-5327 for more information about the Letairis REMS Program.

Please see the accompanying patient Medication Guide and full Prescribing Information, including **BOXED WARNING**, for more complete information.

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LETAIRIS RISK EVALUATION AND MITIGATION STRATEGY (REMS)

Letairis REMS Program Guide for Females Who Can Get Pregnant

This guide is part of an FDA-approved REMS.

Letairis® ambrisentan 5 mg and 10 mg Tablets

Reference ID: 3650027

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Information for Females Who Can Get Pregnant

Information for Females Who Can Get Pregnant

What is Letairis?

Letairis is a prescription medicine to treat pulmonary arterial hypertension (PAH), which is high blood pressure in the arteries of your lungs. Letairis can improve your ability to exercise and it can help slow down the worsening of your physical condition and symptoms.

What are the serious risks of Letairis?

Letairis can cause serious birth defects if taken during pregnancy. Females must not be pregnant when they start taking Letairis or become pregnant while taking Letairis, or for 1 month after stopping Letairis.

What is the Letairis Risk Evaluation and Mitigation Strategy (REMS) Program?

Because of the risk of serious birth defects, the FDA has required a special program called a Risk Evaluation and Mitigation Strategy (REMS) for Letairis. The purpose of the Letairis REMS Program is to make sure the benefits of Letairis outweigh the risks. All females must enroll in the Letairis REMS Program to receive Letairis. Specific requirements apply to females who can get pregnant.

To receive Letairis:

1) You must talk with your doctor to ensure the benefits outweigh the risks of Letairis
2) You must agree to all of the requirements of the Letairis REMS Program. These requirements include monthly pregnancy tests and use of appropriate birth control while taking Letairis and for 1 month after stopping Letairis
3) Your doctor will enroll you in the Letairis REMS Program
4) Your prescription will be mailed to you from a Certified Pharmacy that you and your doctor will choose

How do I enroll in the Letairis REMS Program?

Follow these steps with your doctor:

- Read all the patient information about Letairis and the Letairis REMS Program included in this guide or on the Letairis REMS Program website, **www.letairisrems.com**
- Talk with your doctor to ensure the benefits outweigh the risks of Letairis
- Ask questions. Make sure you understand what you need to do to enroll and take part in the Letairis REMS Program. Make sure you know how to receive and take Letairis
- You and your doctor choose a Certified Pharmacy to supply Letairis. In some cases your insurance company may need you to use a specific Certified Pharmacy
- You and your doctor fill out the *Patient Enrollment and Consent Form*. After you read and sign it, your doctor sends it to the Letairis REMS Coordinating Center

What are the Letairis REMS Program requirements for me?

You are considered to be a female who can get pregnant if you have entered puberty, have a uterus, and have not passed through Menopause.

To receive Letairis, you must:

- Have a negative pregnancy test before you start taking Letairis and before you receive your refills. Your doctor orders the pregnancy tests for you. Your Certified Pharmacy will call you and ask if you have taken this test before shipping your refill
- **Be sure you take your monthly pregnancy tests as ordered by your doctor. You may not receive your Letairis refill on time if you do not take your monthly pregnancy tests**

Do not have unprotected sex. Use appropriate birth control during your Letairis treatment and for 1 month after stopping your Letairis treatment because the medicine may still be in your body. Page 5 of this guide shows your birth control options.

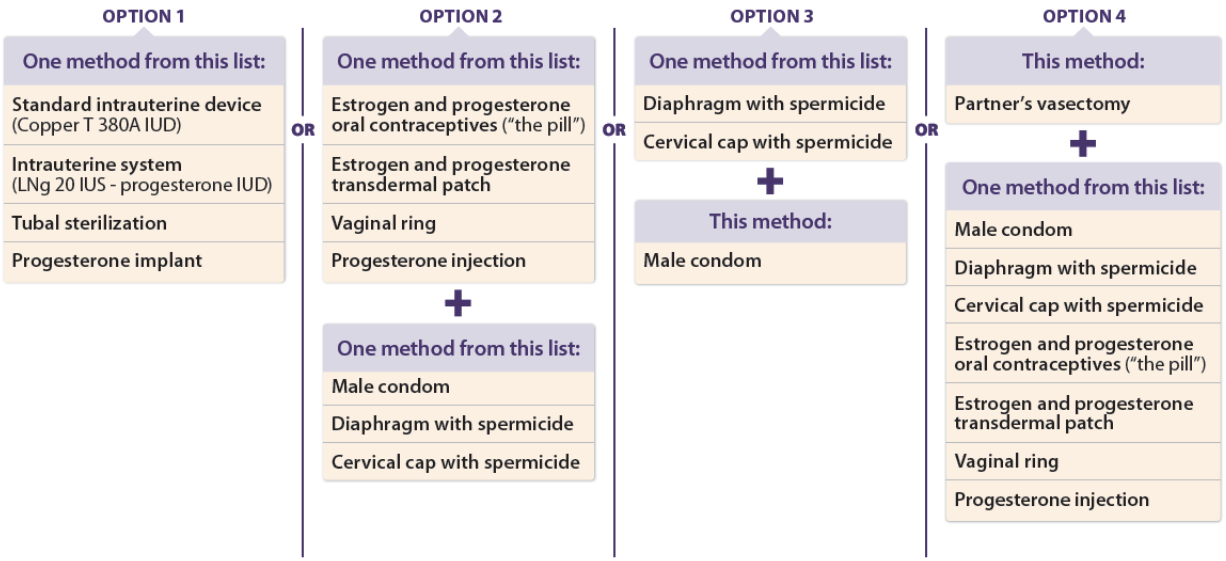
Talk to your doctor or pharmacist right away if you have unprotected sex, if you think your birth control has failed, or if you think you may be pregnant. Your doctor may tell you to use emergency birth control. Do not wait until your next appointment to tell your doctor if you miss your menstrual period or if you think you may be pregnant.

What are my birth control options?

Your doctor will talk to you about your birth control options. Use the diagram on the next page to help decide what birth control options are best for you. Talk to your doctor if you have questions about your birth control options. Tell your doctor if you want to change your birth control method.

You may choose from the four options listed on the next page. More than one birth control method might be needed every time you have sex (intercourse).

Your birth control options



Reference ID: 3650027

How will I receive my Letairis?

Certified Pharmacies provide products and services for patients with certain diseases. Only Certified Pharmacies can provide Letairis to you. In some cases, your insurance company may require you to use a specific Certified Pharmacy.

Your Certified Pharmacy ships your Letairis refill to you. Before each shipment, you will be called to confirm that you have taken a monthly pregnancy test before refilling your prescription. **It is important that your Certified Pharmacy is able to contact you in order to avoid delays in your refills.**

For a list of participating Certified Pharmacies, visit **www.letairisrems.com.**

If you have questions or concerns about Letairis, talk to your doctor. Please visit **www.letairisrems.com** or call **1-866-664-5327** for more information about the Letairis REMS Program.

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ambrisentan
5 mg and 10 mg Tablets

Letairis Patient Enrollment and Consent Form

Fax this form and all patient insurance information, including drug benefit cards (front and back), to: 1-888-882-4035

1 Specialty Pharmacy

Select a preferred Certified Pharmacy:

__Accredo __Aetna Specialty Pharmacy __CIGNA Tel-Drug __CuraScript __CVS Caremark __Exactus Pharmacy Solutions __Kaiser Specialty Pharmacy__ OptumRx __*Right*Source Specialty Pharmacy __Walgreens Specialty Pharmacy

2 Patient Information (PLEASE PR NT)

First Name: _____ Middle Initial: _____ Last Name: _____
Address: _____ City: _____ State: _____ ZIP: _____
Birthdate: ____/____/____ Gender: __M __F Preferred Time to Contact: __Day __Evening
Phone: (____) _____ Alternate Phone: (____)_____ E-mail: _____
Alternate Contact Name: _____Phone: (____)_____
Relationship: _____

3 Written Permission to Share Information

I allow my healthcare providers and health plans to share personal and medical information about me with Gilead and its agents and contractors ("Gilead"). I allow Gilead to use and share this information to: 1) communicate with me, my healthcare providers and health plans about my medical care; 2) provide support services, including providing Letairis® (ambrisentan) to me and planning laboratory testing for me; 3) learn how well Letairis, the Letairis REMS, or LEAP program is working; and 4) contact me so that I may receive educational materials about Letairis, the Letairis REMS, or the LEAP program.

Once my health information has been shared with Gilead, federal privacy laws may no longer protect it. This means that Gilead can give it to others, such as the Food and Drug Administration (FDA), to learn if the Letairis REMS Program is being run properly as required by law. I understand that my pharmacy may receive payment in connection for disclosing my health information to Gilead for the purposes allowed under this authorization. I may also cancel my permission at any time by writing a letter to Gilead and faxing to 1-888-882-4035 or by calling 1-866-664-5327. If I cancel, Gilead will stop using or sharing my information for the reasons listed above, except as required by law to end my participation in the Letairis REMS Program. If I am a female and not enrolled in the Letairis REMS Program, I will no longer be able to receive Letairis. If I do not sign this form, I understand my eligibility for health plan benefits and treatment by my doctor will not change. I am allowed a copy of this signed agreement. My written permission ends 10 years from the date I signed it.

REQUIRED FOR ALL PATIENTS	Patient or Parent/Guardian Signature:	Date:

4 Female Patient Agreement

For all Females: I acknowledge that I have been counseled that Letairis is only available through a restricted distribution program under an FDA-required Risk Evaluation and Mitigation Strategy (REMS).

For Females Who Can Get Pregnant: I acknowledge that I have been counseled on the risks of Letairis, including the risk of serious birth defects. I have read the *Letairis Medication Guide* and the *Letairis REMS Program Guide for Females Who Can Get Pregnant*. I understand that I will be contacted by Gilead and/or its agents and contractors to receive counseling on the risk of serious birth defects and the importance of not becoming pregnant, ensure that I have completed pregnancy testing before I start Letairis, monthly before each refill, and for 1 month after stopping Letairis, and obtain information about my pregnancy, if I become pregnant.

For Pre-Pubertal Females: I acknowledge that I have been counseled on the risks of Letairis, including the risk of serious birth defects, and that I have read the *Letairis Medication Guide*. Parent or guardian must sign below.

REQUIRED FOR ALL FEMALE PATIENTS	Patient or Parent/Guardian Signature:	Date:

5 Prescriber Information (PLEASE PRINT)

First Name: _____ Last Name: _____State License #: _____
Address: _____ City: _____ State: _____ ZIP: _____
Phone: (____) _____ Fax: (____) _____ NPI #: _____

Office Contact (First and Last Name):_____ E-mail:_____

6 Prescription

LETAIRIS: __5 mg tablets (30 tablets) __10 mg tablets (30 tablets) __PO __QD Refills: _____

Instructions: _____

Ship to: __Patient Home (address listed above) __Prescriber Office (address listed above) __Other (please indicate below)

Name: _____ Address: _____

City: _____State: _____ ZIP: _____ Phone: (____) _____

7 Statement of Medical Necessity

Diagnosis: Pulmonary Arterial Hypertension (This is for insurance purposes only, not to suggest approved uses or indications. Please select one category below.)

__Familial (ICD 416.0) __Idiopathic (ICD 416.0)

__Scleroderma (ICD 710.1) __HIV (ICD 042 _____)

__Lupus (ICD 710.0) __Portal Hypertension (ICD 572.3)

__Congenital Heart Defects (ICD 745. _____) __Other: _____ (ICD _____)

8 Prescriber Authorization

For female patients, please indicate the patient's current reproductive status below Only 1 box should be checked. (Please see definitions of these terms on the following page)

Female of Reproductive Potential

Has a negative pregnancy test been confirmed prior to prescribing Letairis?

__ Yes

__ No

OR

Female of Non-Reproductive Potential (choose one below)

__ Pre-Pubertal Female

__ Post-Menopausal Female

__ Other medical reasons for permanent, irreversible infertility

I certify that for female patients, I have provided the appropriate counseling and Letairis REMS materials, and I will continue to fulfill my obligations under the Letairis REMS Program as outlined on page 2 of this form.

By signing, I certify that the above therapy is medically necessary.

REQUIRED FOR ALL PRESCRIBERS	Prescriber Signature: X	Date:

8 Prescriber Authorization (continued)

Definitions

Females of Reproductive Potential

- Females of Reproductive Potential include girls who have entered puberty and all women who have a uterus and have not passed through Menopause (as defined below).
- For the purposes of REMS, puberty includes those girls who are at least Tanner Stage 3 and have not yet had a menses (premenarchal).

Females of Non-Reproductive Potential

- Pre-Pubertal Females: Females who are at Tanner Stages 1 and 2 are not considered to be of reproductive potential
- Post-Menopausal Females: Females who have passed through Menopause (as defined below)
- Other medical reasons for permanent, irreversible infertility

Menopause

Menopause is defined as 12 months of spontaneous amenorrhea (not amenorrhea induced by a medical condition or medical therapy) or postsurgical from bilateral oophorectomy.

Prescriber obligations under the Letairis REMS Program

For All Females

- I acknowledge that I have counseled the patient (and parent/guardian when appropriate) that Letairis is available only through a restricted distribution program under an FDA-required REMS.
- I will evaluate the patient and agree to document any change in reproductive potential status by submitting a *Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form* within 10 business days of becoming aware of the change.

For Females of Reproductive Potential

- I acknowledge that I have counseled the patient (and parent/guardian when appropriate) on the risks of Letairis, including the risk of serious birth defects, and that I have reviewed the *Letairis Medication Guide* and the *Letairis REMS Program Guide for Females Who Can Get Pregnant* with the patient (and parent/guardian when appropriate).
- I will order and review pregnancy tests prior to initiation of Letairis treatment, monthly during treatment, and for 1 month after stopping treatment in accordance with the Letairis REMS Program.

For Pre-Pubertal Females

- I acknowledge that I have counseled the patient and parent/guardian on the risks of Letairis, including the risk of serious birth defects, and that I have reviewed the *Letairis Medication Guide* with the patient and parent/guardian.
- I will evaluate the patient's reproductive potential status, verify reproductive potential status annually for Pre-Pubertal Females who are at least 8 years of age and older, and agree to report any change in reproductive potential status on a *Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form* within 10 business days of becoming aware of the change.

9 Fax this enrollment form and all patient insurance information, including drug benefit cards (front and back), to 1-888-882-4035.

Please visit **www.letairisrems.com** or call **1-866-664-5327** for more information about the Letairis REMS Program.

Please see accompanying patient Medication Guide and full Prescribing Information, including **BOXED WARNING**.

This form is part of an FDA-approved REMS.

Letairis Patient Enrollment and Consent Form

Enroll Patient in *LabSync*®: __Yes __No

Fax this form and all patient insurance information, including drug benefit cards (front and back), to: 1-888-882-4035

1 Specialty Pharmacy

Select a preferred Certified Pharmacy:

__Accredo __Aetna Specialty Pharmacy __CIGNA Tel-Drug __CuraScript __CVS Caremark __Exactus Pharmacy Solutions __Kaiser Specialty Pharmacy__ OptumRx __*Right*Source Specialty Pharmacy __Walgreens Specialty Pharmacy

2 Patient Information (PLEASE PR NT)

First Name: _____ Middle Initial: _____ Last Name: _____
Address: _____ City: _____ State: _____ ZIP: _____
Birthdate: ____/____ /____ Gender: __M __F Preferred Time to Contact: __Day __Evening
Phone: (____) _____ Alternate Phone: (____)_____ E-mail: _____
Alternate Contact Name: _____Phone: (____)_____
Relationship: _____

3 Written Permission to Share Information

I allow my healthcare providers and health plans to share personal and medical information about me with Gilead and its agents and contractors ("Gilead"). I allow Gilead to use and share this information to: 1) communicate with me, my healthcare providers and health plans about my medical care; 2) provide support services, including providing Letairis® (ambrisentan) to me and planning laboratory testing for me; 3) learn how well Letairis, the Letairis REMS, or LEAP program is working; and 4) contact me so that I may receive educational materials about Letairis, the Letairis REMS, or the LEAP program.

I understand that I may choose not to take part in *LabSync*, but I may still take part in Letairis support services. Once my health information has been shared with Gilead, federal privacy laws may no longer protect it. This means that Gilead can give it to others, such as the Food and Drug Administration (FDA), to learn if the Letairis REMS Program is being run properly as required by law. I understand that my pharmacy may receive payment in connection for disclosing my health information to Gilead for the purposes allowed under this authorization. I may also cancel my permission at any time by writing a letter to Gilead and faxing to 1-888-882-4035 or by calling 1-866-664-5327. If I cancel, Gilead will stop using or sharing my information for the reasons listed above, except as required by law to end my participation in the Letairis REMS Program. If I am a female and not enrolled in the Letairis REMS Program, I will no longer be able to receive Letairis. If I do not sign this form, I understand my eligibility for health plan benefits and treatment by my doctor will not change. I am allowed a copy of this signed agreement. My written permission ends 10 years from the date I signed it.

REQUIRED FOR ALL PATIENTS	Patient or Parent/Guardian Signature:	Date:

4 Female Patient Agreement

For all Females: I acknowledge that I have been counseled that Letairis is only available through a restricted distribution program under an FDA-required Risk Evaluation and Mitigation Strategy (REMS).

For Females Who Can Get Pregnant: I acknowledge that I have been counseled on the risks of Letairis, including the risk of serious birth defects. I have read the *Letairis Medication Guide* and the *Letairis REMS Program Guide for Females Who Can Get Pregnant*. I understand that I will be contacted by Gilead and/or its agents and contractors to receive counseling on the risk of serious birth defects and the importance of not becoming pregnant, ensure that I have completed pregnancy testing before I start Letairis, monthly before each refill, and for 1 month after stopping Letairis, and obtain information about my pregnancy, if I become pregnant.

For Pre-Pubertal Females: I acknowledge that I have been counseled on the risks of Letairis, including the risk of serious birth defects, and that I have read the *Letairis Medication Guide*. Parent or guardian must sign below.

REQUIRED FOR ALL FEMALE PATIENTS	Patient or Parent/Guardian Signature:	Date:

5 Prescriber Information (PLEASE PRINT)

First Name: _____ Last Name: _____State License #: _____
Address: _____ City: _____ State: _____ ZIP: _____
Phone: (____) _____ Fax: (____) _____ NPI #: _____

Office Contact (First and Last Name):_____ E-mail:_____

6 Prescription

LETAIRIS: __5 mg tablets (30 tablets) __10 mg tablets (30 tablets) __PO __QD Refills: _____

Instructions: _____

Ship to: __Patient Home (address listed above) __Prescriber Office (address listed above) __Other (please indicate below)

Name: _____ Address: _____

City: _____State: _____ ZIP: _____
Phone: (____) _____

7 Statement of Medical Necessity

Diagnosis: Pulmonary Arterial Hypertension (This is for insurance purposes only, not to suggest approved uses or indications. Please select one category below.)

__Familial (ICD 416.0) __Idiopathic (ICD 416.0)

__Scleroderma (ICD 710.1) __HIV (ICD 042 _____)

__Lupus (ICD 710.0) __Portal Hypertension (ICD 572.3)

__Congenital Heart Defects (ICD 745. _____) __Other: _____ (ICD _____)

8 Prescriber Authorization

For female patients, please indicate the patient's current reproductive status below. Only 1 box should be checked. (Please see definitions of these terms on the following page)

Female of Reproductive Potential

Has a negative pregnancy test been confirmed prior to prescribing Letairis?

__ Yes

__ No

OR

Female of Non-Reproductive Potential (choose one below)

__ Pre-Pubertal Female

__ Post-Menopausal Female

__ Other medical reasons for permanent, irreversible infertility

I certify that for female patients, I have provided the appropriate counseling and Letairis REMS materials, and I will continue to fulfill my obligations under the Letairis REMS Program as outlined on page 2 of this form.

I authorize *LabSync* to order laboratory tests and receive laboratory results on my behalf for patients enrolled in the Letairis REMS Program and *LabSync*.

By signing, I certify that the above therapy is medically necessary.

REQUIRED FOR ALL PRESCRIBERS	Prescriber Signature: X	Date:

8 Prescriber Authorization (continued)

Definitions

Females of Reproductive Potential

- Females of Reproductive Potential include girls who have entered puberty and all women who have a uterus and have not passed through Menopause (as defined below).
- For the purposes of REMS, puberty includes those girls who are at least Tanner Stage 3 and have not yet had a menses (premenarchal).

Females of Non-Reproductive Potential

- Pre-Pubertal Females: Females who are at Tanner Stages 1 and 2 are not considered to be of reproductive potential
- Post-Menopausal Females: Females who have passed through Menopause (as defined below)
- Other medical reasons for permanent, irreversible infertility

Menopause

Menopause is defined as 12 months of spontaneous amenorrhea (not amenorrhea induced by a medical condition or medical therapy) or postsurgical from bilateral oophorectomy.

Prescriber obligations under the Letairis REMS Program

For All Females

- I acknowledge that I have counseled the patient (and parent/guardian when appropriate) that Letairis is available only through a restricted distribution program under an FDA-required REMS.
- I will evaluate the patient and agree to document any change in reproductive potential status by submitting a *Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form* within 10 business days of becoming aware of the change.

For Females of Reproductive Potential

- I acknowledge that I have counseled the patient (and parent/guardian when appropriate) on the risks of Letairis, including the risk of serious birth defects, and that I have reviewed the *Letairis Medication Guide* and the *Letairis REMS Program Guide for Females Who Can Get Pregnant* with the patient (and parent/guardian when appropriate).
- I will order and review pregnancy tests prior to initiation of Letairis treatment, monthly during treatment, and for 1 month after stopping treatment in accordance with the Letairis REMS Program.

For Pre-Pubertal Females

- I acknowledge that I have counseled the patient and parent/guardian on the risks of Letairis, including the risk of serious birth defects, and that I have reviewed the *Letairis Medication Guide* with the patient and parent/guardian.
- I will evaluate the patient's reproductive potential status, verify reproductive potential status annually for Pre-Pubertal Females who are at least 8 years of age and older, and agree to report any change in reproductive potential status on a *Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form* within 10 business days of becoming aware of the change.

9 Fax this enrollment form and all patient insurance information, including drug benefit cards (front and back), to 1-888-882-4035.

Please visit **www.letairisrems.com** or call **1-866-664-5327** for more information about the Letairis REMS Program.

Please see accompanying patient Medication Guide and full Prescribing Information, including **BOXED WARNING**.

This form is part of an FDA-approved REMS.

Letairis Patient Enrollment and Consent Form

FOR VA USE ONLY

Fax this form and all patient insurance information, including drug benefit cards (front and back), to: 1-888-882-4035

1 Specialty Pharmacy

Select a preferred Certified Pharmacy:

__Accredo

2 Patient Information (PLEASE PR NT)

First Name: _____ Middle Initial: _____ Last Name: _____
Address: _____ City: _____ State: _____ ZIP: _____
Birthdate: ____/____ /____ Gender: __M __F Preferred Time to Contact: __Day __Evening
Phone: (____) _____ Alternate Phone: (____)_____ E-mail: _____
Alternate Contact Name: _____Phone: (____)_____
Relationship: _____

3 Written Permission to Share Information

I allow Veterans Health Care Administration ("VA"), my specialty pharmacy or pharmacies, and my health plans to share personal and medical information about me to Gilead and its agents and contractors ("Gilead"). I allow Gilead to use and share this information to: 1) communicate with me, my healthcare providers and health plans about my medical care; 2) provide support services, including providing Letairis® (ambrisentan) to me; 3) learn how well Letairis, the Letairis REMS, or LEAP program is working; and 4) contact me so that I may receive educational materials about Letairis, the Letairis REMS, or the LEAP program.

Once my health information has been shared with Gilead, federal privacy laws may no longer protect it. This means that Gilead can give it to others, such as the Food and Drug Administration (FDA), to learn if the Letairis REMS Program is being run properly as required by law. I understand that my pharmacy may receive payment in connection for disclosing my health information to Gilead for the purposes allowed under this authorization. I may also cancel my permission at any time by writing a letter to Gilead and faxing to 1-888-882-4035 or by calling 1-866-664-5327. If I cancel, Gilead will stop using or sharing my information for the reasons listed above, except as required by law to end my participation in the Letairis REMS Program. If I am a female and not enrolled in the Letairis REMS Program, I will no longer be able to receive Letairis. If I do not sign this form, I understand my eligibility for health plan benefits and treatment by my doctor will not change. I am allowed a copy of this signed agreement. My written permission ends 10 years from the date I signed it.

REQUIRED FOR ALL PATIENTS	Patient or Parent/Guardian Signature:	Date:

4 Female Patient Agreement

For all Females: I acknowledge that I have been counseled that Letairis is only available through a restricted distribution program under an FDA-required Risk Evaluation and Mitigation Strategy (REMS).

For Females Who Can Get Pregnant: I acknowledge that I have been counseled on the risks of Letairis, including the risk of serious birth defects. I have read the *Letairis Medication Guide* and the *Letairis REMS Program Guide for Females Who Can Get Pregnant*. I understand that I will be contacted by Gilead and/or its agents and contractors to receive counseling on the risk of serious birth defects and the importance of not becoming pregnant, ensure that I have completed pregnancy testing before I start Letairis, monthly before each refill, and for 1 month after stopping Letairis, and obtain information about my pregnancy, if I become pregnant.

For Pre-Pubertal Females: I acknowledge that I have been counseled on the risks of Letairis, including the risk of serious birth defects, and that I have read the *Letairis Medication Guide*. Parent or guardian must sign below.

REQUIRED FOR ALL FEMALE PATIENTS	Patient or Parent/Guardian Signature:	Date:

5 Prescriber Information (PLEASE PRINT)

First Name: _____ Last Name: _____State License #: _____
Address: _____ City: _____ State: _____ ZIP: _____
Phone: (____) _____ Fax: (____) _____ NPI #: _____

Office Contact (First and Last Name):_____ E-mail:_____

6 Prescription

LETAIRIS: __5 mg tablets (30 tablets) __10 mg tablets (30 tablets) __PO __QD Refills: _____

Instructions: _____

Ship to: __Patient Home (address listed above) __Prescriber Office (address listed above) __Other (please indicate below)

Name: _____ Address: _____

City: _____State: _____ ZIP: _____ Phone: (____) _____

7 Statement of Medical Necessity

Diagnosis: Pulmonary Arterial Hypertension (This is for insurance purposes only, not to suggest approved uses or indications. Please select one category below.)

__Familial (ICD 416.0) __Idiopathic (ICD 416.0)

__Scleroderma (ICD 710.1) __HIV (ICD 042 _____)

__Lupus (ICD 710.0) __Portal Hypertension (ICD 572.3)

__Congenital Heart Defects (ICD 745. _____) __Other: _____ (ICD _____)

8 Prescriber Authorization

For female patients, please indicate the patient's current reproductive status below. Only 1 box should be checked. (Please see definitions of these terms on the following page)

Female of Reproductive Potential

Has a negative pregnancy test been confirmed prior to prescribing Letairis?

__ Yes

__ No

OR

Female of Non-Reproductive Potential (choose one below)

__ Pre-Pubertal Female

__ Post-Menopausal Female

__ Other medical reasons for permanent, irreversible infertility

I certify that for female patients, I have provided the appropriate counseling and Letairis REMS materials, and I will continue to fulfill my obligations under the Letairis REMS Program as outlined on page 2 of this form.

By signing, I certify that the above therapy is medically necessary.

REQUIRED FOR ALL PRESCRIBERS	Prescriber Signature: X	Date:

8 Prescriber Authorization (continued)

Definitions

Females of Reproductive Potential

- Females of Reproductive Potential include girls who have entered puberty and all women who have a uterus and have not passed through Menopause (as defined below).
- For the purposes of REMS, puberty includes those girls who are at least Tanner Stage 3 and have not yet had a menses (premenarchal).

Females of Non-Reproductive Potential

- Pre-Pubertal Females: Females who are at Tanner Stages 1 and 2 are not considered to be of reproductive potential
- Post-Menopausal Females: Females who have passed through Menopause (as defined below)
- Other medical reasons for permanent, irreversible infertility

Menopause

Menopause is defined as 12 months of spontaneous amenorrhea (not amenorrhea induced by a medical condition or medical therapy) or postsurgical from bilateral oophorectomy.

Prescriber obligations under the Letairis REMS Program

For All Females

- I acknowledge that I have counseled the patient (and parent/guardian when appropriate) that Letairis is available only through a restricted distribution program under an FDA-required REMS.
- I will evaluate the patient and agree to document any change in reproductive potential status by submitting a *Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form* within 10 business days of becoming aware of the change.

For Females of Reproductive Potential

- I acknowledge that I have counseled the patient (and parent/guardian when appropriate) on the risks of Letairis, including the risk of serious birth defects, and that I have reviewed the *Letairis Medication Guide* and the *Letairis REMS Program Guide for Females Who Can Get Pregnant* with the patient (and parent/guardian when appropriate).
- I will order and review pregnancy tests prior to initiation of Letairis treatment, monthly during treatment, and for 1 month after stopping treatment in accordance with the Letairis REMS Program.

For Pre-Pubertal Females

- I acknowledge that I have counseled the patient and parent/guardian on the risks of Letairis, including the risk of serious birth defects, and that I have reviewed the *Letairis Medication Guide* with the patient and parent/guardian.
- I will evaluate the patient's reproductive potential status, verify reproductive potential status annually for Pre-Pubertal Females who are at least 8 years of age and older, and agree to report any change in reproductive potential status on a *Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form* within 10 business days of becoming aware of the change.

9 Fax this enrollment form and all patient insurance information, including drug benefit cards (front and back), to 1-888-882-4035.

Please visit **www.letairisrems.com** or call **1-866-664-5327** for more information about the Letairis REMS Program.

Please see accompanying patient Medication Guide and full Prescribing Information, including **BOXED WARNING**.

This form is part of an FDA-approved REMS.

Letairis Risk Evaluation and Mitigation Strategy (REMS) Program

Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form

Fax form to: 1-888-882-4035

Complete this form to:

1. Change the reproductive status of any female patient, or
2. Complete the annual verification of reproductive potential status for Pre-Pubertal Females, 8 years of age or older

Prescriber must complete this form within 10 business days of awareness of the change in reproductive potential status.

1 Patient Information (PLEASE PRINT)

Patient Letairis REMS ID: _____

First Name: _____ Middle Initial: _____ Last Name: _____

Address: _____ City: _____ State: _____ ZIP: _____

Birthdate: ____/____ /____ Phone: (____) _____

2 Prescriber Information (PLEASE PRINT)

Office Contact and E-mail Address: _____

First Name: _____ Last Name: _____ State License #: _____

Address: _____ City: _____ State: ____ ZIP: _____

Phone: (____) _____ Fax: (____) _____ NPI #: _____

Definitions of Reproductive Potential Status:

Females of Reproductive Potential

- Females of Reproductive Potential include girls who have entered puberty and all women who have a uterus and have not passed through Menopause (as defined below).
- For the purposes of this REMS, puberty includes those girls who are at least Tanner Stage 3 and have not yet had a menses (premenarchal).

Females of Non-Reproductive Potential

- Pre-Pubertal Females: Females who are at Tanner Stages 1 and 2 are not considered to be of reproductive potential.
- Post-Menopausal Female: Females who have passed through Menopause (as defined below).
- Other medical reasons for permanent, irreversible infertility.

Menopause

Menopause is defined as 12 months of spontaneous amenorrhea (not amenorrhea induced by a medical condition or medical therapy) or post-surgical from bilateral oophorectomy.

3 Please select the most appropriate reason for submitting this form.

Change in Status

- **Based on definitions of reproductive potential status, patient is (please check one):**

  ___ Female of Reproductive Potential

  ___ Female of Non-Reproductive Potential – Patient is pre-pubertal

  ___ Female of Non-Reproductive Potential – Patient is post-menopausal

  ___ Female of Non-Reproductive Potential – Other medical reasons for permanent, irreversible infertility

- **Reason for change in classification (please check one):**

  ____ Physiological transition

  ____ Medical/surgical (please specify):_____

  ____ Other (please specify):_____

Annual Verification

____ Patient remains a Pre-Pubertal Female (8 years of age or older)

REQUIRED	**By signing, I certify that the patient's reproductive potential status and reason for submitting this form are accurately noted above.** Prescriber Signature: X	Date:

Please visit **www.letairisrems.com** or call **1-866-664-5327** for more information about the Letairis REMS Program.

This form is part of an FDA-approved REMS.

GILEAD

Letairis® ambrisentan 5 mg and 10 mg Tablets

The Letairis Risk Evaluation and Mitigation Strategy (REMS) Program

A Risk Evaluation and Mitigation Strategy is a strategy to manage known or potential serious risks associated with a drug product and is required by the Food and Drug Administration (FDA) to ensure that the benefits of the drug outweigh its risks.

The purpose of the Letairis REMS Program is to:

- Inform prescribers, patients, and pharmacists about the risk of serious birth defects and safe-use conditions for Letairis
- Minimize the risk of fetal exposure and adverse fetal outcomes in Females of Reproductive Potential prescribed Letairis
    - Females who are pregnant must not be prescribed Letairis
    - Females taking Letairis must not become pregnant

Letairis
ambrisentan
5 mg and 10 mg Tablets

IMPORTANT SAFETY INFORMATION FULL PRESCRIBING INFORMATION MEDICATION GUIDE

FOR PRESCRIBERS (ANNOTATED TEXT…WILL NOT APPEAR ON LIVE SITE)

Download Letairis REMS Materials >

In order to ensure that Letairis is prescribed and taken safely, Gilead has worked with the FDA to develop materials for the Letairis REMS Program to inform prescribers and patients about the risk of serious birth defects.

Letairis REMS Program Prescriber Materials

Prescriber Guide to the Letairis REMS Program
Prescriber Enrollment and Agreement Form
Patient Enrollment and Consent Form
Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form

Letairis REMS Program Patient Education Materials
Letairis REMS Program Guide for Females Who Can Get Pregnant
Get ADOBE® READER®

Overview of the Letairis REMS Program

- Prescribers must enroll in the Letairis REMS Program and comply with the Letairis REMS Program requirements to prescribe Letairis
- All female patients must enroll in the Letairis REMS Program to receive Letairis
- Prescribers must educate and counsel Females of Reproductive Potential and Pre-Pubertal Females as described in the *Prescriber Guide to the Letairis REMS Program.* The parent/guardian of the Pre-Pubertal Female must also be educated and counseled on the risks of Letairis.
- Required pregnancy testing for Females of Reproductive Potential prior to writing a prescription for Letairis and monthly thereafter, including 1 month after stopping treatment with Letairis
- Letairis is only available through a restricted distribution program

Changes to the Letairis REMS Program (October 2014)

- New definition of Female of Non-Reproductive Potential
- Revised form*: Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form*

- **The following is a list of participating Certified Pharmacies:**

Accredo
Aetna Specialty Pharmacy
CIGNA Tel-Drug
CuraScript
CVS Caremark
Exactus Pharmacy Solutions
Kaiser Specialty Pharmacy
OptumRx
*Right*Source Specialty Pharmacy
Walgreens Specialty Pharmacy

Letairis
ambrisentan
5 mg and 10 mg Tablets

IMPORTANT SAFETY INFORMATION FULL PRESCRIBING INFORMATION
MEDICATION GUIDE

FOR PATIENTS (ANNOTATED TEXT…WILL NOT APPEAR ON LIVE SITE)

Welcome to the Letairis Risk Evaluation and Mitigation Strategy Program

What is the Letairis REMS Program?

Because of the risk of serious birth defects, the FDA has required a special program called a Risk Evaluation and Mitigation Strategy (REMS) for Letairis. The purpose of the Letairis REMS Program is to make sure the benefits of Letairis outweigh the risks. All females must enroll in the Letairis REMS Program to receive Letairis; however, specific requirements apply to females who can get pregnant.

For Female Patients to receive Letairis:

1) You must talk with your doctor to ensure the benefits outweigh the risks of Letairis
2) You must agree to all of the requirements of the Letairis REMS Program. For women who can get pregnant, these requirements include monthly pregnancy tests and use of appropriate birth control while taking Letairis and for 1 month after stopping Letairis
3) Your doctor will enroll you in the Letairis REMS Program
4) Your prescription will be mailed to you from a Certified Pharmacy that you and your doctor will choose

For women who can get pregnant, learn more about the Letairis REMS Program. Download this helpful guide.

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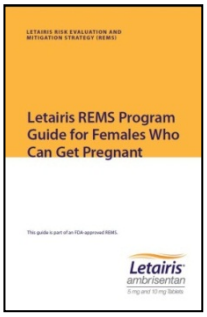


GILEAD

Medication Guide
Letairis® (le-TAIR-is)
(ambrisentan)
Tablets

Read this Medication Guide before you start taking Letairis and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking with your doctor about your medical condition or your treatment.

What is the most important information I should know about Letairis?

Serious birth defects.

Letairis can cause serious birth defects if taken during pregnancy.

- **Females must not be pregnant when they start taking Letairis or become pregnant during treatment with Letairis.**
- Females who are able to get pregnant must have a negative pregnancy test before beginning treatment with Letairis, each month during treatment with Letairis, and one month after stopping Letairis. Talk to your doctor about your menstrual cycle. Your doctor will decide when to do the tests, and order the tests for you depending on your menstrual cycle.
    - Females who <u>are able</u> to get pregnant are females who:
        - Have entered puberty, even if they have not started their period, **and**
        - Have a uterus, **and**
        - Have not gone through menopause (have not had a period for at least 12 months for natural reasons, or who have had their ovaries removed)
    - Females who <u>are not able</u> to get pregnant are females who:
        - Have not yet entered puberty, **or**
        - Do not have a uterus, **or**
        - Have gone through menopause (have not had a period for at least 12 months for natural reasons, or who have had their ovaries removed)

Females who are able to get pregnant must use two acceptable forms of birth control, during treatment with Letairis, and for one

month after stopping Letairis because the medicine may still be in the body.

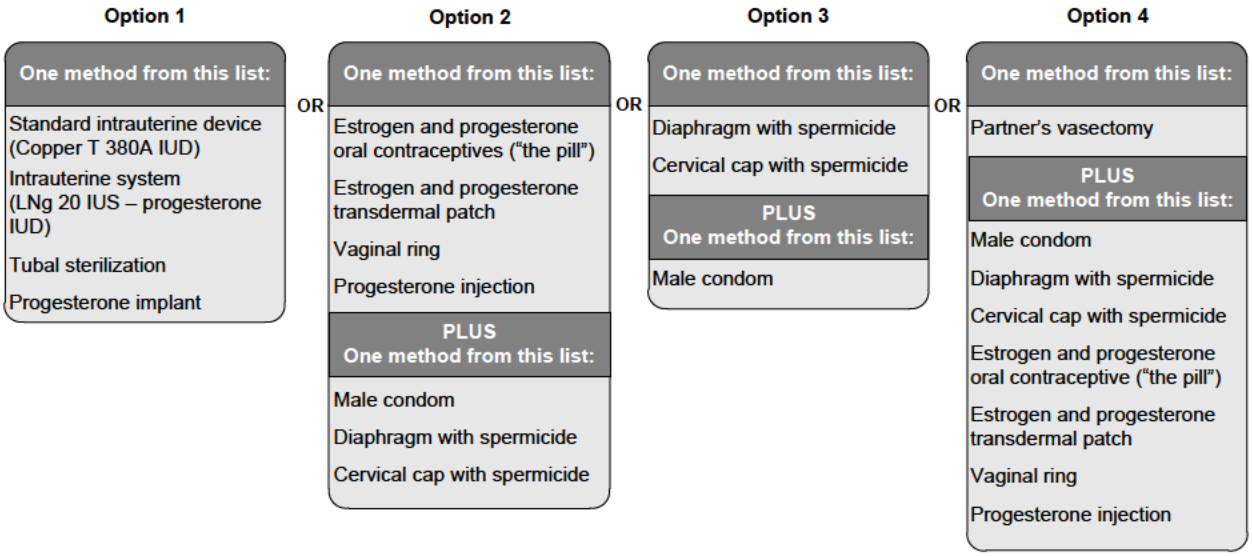
- If you have had a tubal sterilization or have an IUD (intrauterine device) or progesterone implant, these methods can be used alone and no other form of birth control is needed.

- Talk with your doctor or gynecologist (a doctor who specializes in female reproduction) to find out about options for acceptable forms of birth control that you may use to prevent pregnancy during treatment with Letairis.

- If you decide that you want to change the form of birth control that you use, talk with your doctor or gynecologist to be sure that you choose another acceptable form of birth control.

See the chart below for Acceptable Birth Control Options during treatment with Letairis.

Acceptable Birth Control Options



- **Do not have unprotected sex. Talk to your doctor or pharmacist right away if you have unprotected sex or if you think your birth control has failed. Your doctor may tell you to use emergency birth control.**

- **Tell your doctor right away if you miss a menstrual period or think you may be pregnant for any reason.**

If you are the parent or caregiver of a female child who started taking Letairis before reaching puberty, you should check your child regularly to see if she is developing signs of puberty. Tell your doctor right away if you notice that she is developing breast buds or any pubic hair. Your doctor should decide if your child has reached puberty**. Your child may reach puberty before having her first menstrual period.**

Females can only receive Letairis through a restricted program called the Letairis Risk Evaluation and Mitigation Strategy (REMS) program. If you are a female who can get pregnant, you must talk to your doctor, understand the benefits and risks of Letairis, and agree to all of the instructions in the Letairis REMS program.

Males can receive Letairis without taking part in the Letairis REMS program.

What is Letairis?

- Letairis is a prescription medicine to treat pulmonary arterial hypertension (PAH), which is high blood pressure in the arteries of your lungs.
- Letairis can improve your ability to exercise and it can help slow down the worsening of your physical condition and symptoms.
- It is not known if Letairis is safe and effective in children.

Who should not take Letairis?

Do not take Letairis if:

- **you are pregnant, plan to become pregnant, or become pregnant during treatment with Letairis. Letairis can cause serious birth defects.** (See the Medication Guide section above called "What is the most important information I should know about Letairis?") Serious birth defects from Letairis happen early in pregnancy.
- you have a condition called Idiopathic Pulmonary Fibrosis (IPF).

Tell your doctor about all your medical conditions and all the medicines you take including prescription and nonprescription medicines. Letairis and other medicines may affect each other causing side effects. Do not start any new medicines until you check with your doctor.

Especially tell your doctor if you take the medicine cyclosporine (Gengraf, Neoral, Sandimmune). Your doctor may need to change your dose of Letairis. You should not take more than 5 mg of Letairis each day if you also take cyclosporine.

How should I take Letairis?

Letairis will be mailed to you by a certified pharmacy. Your doctor will give you complete details.

- Take Letairis exactly as your doctor tells you. Do not stop taking Letairis unless your doctor tells you.
- You can take Letairis with or without food.
- Do not split, crush or chew Letairis tablets.
- It will be easier to remember to take Letairis if you take it at the same time each day.
- If you take more than your regular dose of Letairis, call your doctor right away.
- If you miss a dose, take it as soon as you remember that day. Take your next dose at the regular time. Do not take two doses at the same time to make up for a missed dose.

What should I avoid while taking Letairis?

- **Do not get pregnant** while taking Letairis. (See the serious birth defects section of the Medication Guide above called "What is the most important information I should know about Letairis?") If you miss a menstrual period, or think you might be pregnant, call your doctor right away.

It is not known if Letairis passes into your breast milk. You should not breastfeed if you are taking Letairis. Talk to your doctor about the best way to feed your baby if you take Letairis.

What are the possible side effects of Letairis?

Letairis can cause serious side effects including:

- **Serious birth defects.** (See "What is the most important information I should know about Letairis?")
- **Swelling all over the body** (fluid retention) can happen within weeks after starting Letairis. Tell your doctor right away if you have any unusual weight gain, tiredness, or trouble breathing while taking Letairis. These may be symptoms of a serious health problem. You may need to be treated with medicine or need to go to the hospital.
- **Sperm count reduction.** Reduced sperm counts have been observed in some men taking a drug similar to Letairis, an effect which might impair their ability to father a child. Tell your doctor if remaining fertile is important to you.
- **Low red blood cell levels** (anemia) can happen during the first weeks after starting Letairis. If this happens, you may need a blood transfusion. Your doctor will do blood tests to check your red blood cells before starting Letairis. Your doctor may also do these tests during treatment with Letairis.

The most common side effects of Letairis are:

- Swelling of hands, legs, ankles and feet (peripheral edema)
- Stuffy nose (nasal congestion)
- Inflamed nasal passages (sinusitis)
- Hot flashes or getting red in the face (flushing)

Some medicines that are like Letairis can cause liver problems. Tell your doctor if you get any of these symptoms of a liver problem while taking Letairis:

- loss of appetite
- nausea or vomiting
- fever
- achiness
- generally do not feel well
- pain in the upper right stomach (abdominal) area
- yellowing of your skin or the whites of your eyes
- dark urine
- itching

Tell your doctor if you have any side effect that bothers you or that does not go away. These are not all of the possible side effects of Letairis. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store Letairis?

Store Letairis at room temperature between 68 °F to 77 °F (20 °C to 25 °C), in the package it comes in.

Keep Letairis and all medicines out of the reach of children.

General information about Letairis

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use Letairis for a condition for which it was not prescribed. Do not give Letairis to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about Letairis. If you would like more information, ask your doctor. You can ask

your doctor or pharmacist for information about Letairis that is written for health professionals.

For more information, call 1-866-664-5327 or visit www.letairis.com or www.gilead.com.

What are the ingredients in Letairis?

Active ingredient: ambrisentan.

Inactive Ingredients: croscarmellose sodium, lactose monohydrate, magnesium stearate and microcrystalline cellulose. The tablets are film-coated with a coating material containing FD&C Red #40 aluminum lake, lecithin, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Gilead Sciences, Inc., Foster City, CA 94404

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